

# **Exhibit 14**

# Ovarian Cancer and Talc

## A Case-Control Study

**EXHIBIT**

P1.48 - KATHLEEN WILLE

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DANIEL W. CRAMER, MD,\*†‡ WILLIAM R. WELCH, MD,§ ROBERT E. SCULLY, MD,||  
AND CAROL A. WOJCIECHOWSKI, RN‡

Opportunities for genital exposure to talc were assessed in 215 white females with epithelial ovarian cancers and in 215 control women from the general population matched by age, race, and residence. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yielded a relative risk of 1.92 ( $P < 0.003$ ) for ovarian cancer associated with these practices. Women who had regularly engaged in both practices had an adjusted relative risk of 3.28 ( $P < 0.001$ ) compared to women with neither exposure. This provides some support for an association between talc and ovarian cancer hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas. The authors also investigated opportunities for potential talc exposure from rubber products such as condoms or diaphragms or from pelvic surgery. No significant differences were noted between cases and controls in these exposures, although the intensity of talc exposure from these sources was likely affected by variables not assessed in this study. *Cancer* 50:372-376, 1982.

**T**HE POSSIBILITY that ovarian cancer may be caused by exposure to certain hydrous magnesium silicates such as talc and asbestos has been raised by several researchers.<sup>1-3</sup> The lack of epidemiologic studies regarding this hypothesis prompted us to investigate talc exposure in a case-control study of ovarian cancer.

### Methods

The cases studied were women with ovarian cancer, diagnosed between November 1978 and September 1981 and identified through the pathology logs or tumor boards of twelve participating hospitals in the Greater Boston area. The study was restricted to English-speaking residents of Massachusetts ranging in age from 18 to 80 years. During the study period, 297 eligible cases were identified. Physicians denied permission to contact their patients in 13 instances. Fourteen patients declined to participate, and 14 other patients had died or moved before they could be contacted.

For each of the 256 interviewed cases, slides of the surgical specimens were reviewed by two authors (W.R.W. or R.E.S.). Eighteen cases were excluded as nonovarian primaries. Each ovarian tumor was classified according to the Histological Classification of Ovarian Tumors of the World Health Organization.<sup>4</sup> The present analysis was restricted to 215 white women with epithelial cancers, including 39 with tumors of borderline malignancy and their matched controls.

Control cases were identified through the Massachusetts Town Books, annual publications that list residents by name, age, and address. Controls were selected randomly from those women who matched cases by precinct of residence, race, and age within two years. Additionally, it was required that a subject be excluded

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This study could not have occurred without the generous participation of many clinicians and institutions in the greater Boston area including: Dr. Emanuel Friedman of the Beth Israel Hospital, Drs. Robert Knapp and Thomas Griffiths of the Brigham and Women's Hospital and Sidney Farber Cancer Institute, Dr. Arthur Hassett of the Brockton Hospital, Dr. Joel Rankin of the Framingham Union Hospital, Dr. Edward Copenhaver of the Lahey Clinic Foundation, Dr. James Nelson of the Massachusetts General Hospital, Dr. Clement Yahia of the New England Deaconess Hospital, Dr. Lalita Gandbhir of the Pondville Hospital, Dr. James Whelton of Saint Elizabeth's Hospital, Dr. Stephen Alpert of the Salem Hospital, Dr. Richard Hunter of the University of Massachusetts Medical School. The superb clerical and technical assistance of Ms. Eileen McManus, Ms. Sally Cassells, and Ms. Christine Peters is also gratefully acknowledged.

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as a control if she had had a bilateral salpingo-oophorectomy, but subjects were not excluded because of prior hysterectomy or other types of pelvic operations. Women who had had pelvic operations were generally confident in their knowledge of whether their ovaries had been removed, but the nature of the operations could not be verified by hospital records in each instance. Women whose statements could not be verified were included or excluded on the basis of their recollection of the surgery. The 215 controls in this study were eventually obtained from a total of 475 potential controls identified through the Town Books. Fifty-six (12%) of the total could not be reached because they had moved, died, or had disconnected or unlisted phones. Twenty-nine (6%) of the total were ineligible because of a history of bilateral salpingo-oophorectomy, while 20 (4%) were of the wrong age or race or did not speak English. Of the total potential controls, 155 (33%) refused to participate. If the 215 cases are characterized as to ease of matching, 121 (56%) cases were matched with no refusals, 58 (27%) were matched after one refusal, and 36 (17%) were matched only after two or more refusals.

Interviews were conducted personally to assess a number of factors from the menstrual and reproductive history, medical and family history, and environmental exposures. This report will deal only with the results of several questions related to potential or definite talc exposure by way of contraceptive practices, operations, or perineal hygiene. Subjects were stratified by potential confounders described below, and adjusted relative risks associated with these exposures were calculated by the Mantel-Haenszel procedure as adapted by Rothman and Boice.<sup>5</sup> To accommodate other confounders as well as the matched design in the data collection, logistic analysis for matched data as described by Breslow *et al.*<sup>6</sup> was also employed.

### Results

The average age (and standard error of the mean, SEM) for cases was 53.2 (1.0) years and for controls,

TABLE 1. Characteristics of Cases and Controls

Characteristic	Cases (Total = 215)		Controls (Total = 215)	
	No.	%	No.	%
Educational level (completed college)	48	22.3	49	22.8
Religion (Roman Catholic)	126	58.6	128	59.5
Marital status (never married)	46	21.4	24	11.2
Nulliparous	78	36.3	39	18.1
Menopausal status (postmenopausal*)	137	63.7	129	60.0

\* Postmenopausal at time of diagnosis for cases or for interview for controls.

53.5 (1.0) years. Table 1 shows other characteristics of subjects. Controls were comparable to cases in educational level and religion. Cases and controls differed significantly in marital status and parity with parity being the more important discriminator between them. Sixty-four percent of the cases were postmenopausal at the time of diagnosis, whereas 60% of controls were postmenopausal. Of these, 15 cases and 20 controls had had an artificial menopause. Parity and menopausal status were considered important potential confounders in this analysis and were adjusted for as described above.

Relative risks associated with potential talc exposure from contamination on rubber products are explored in Table 2. Although surgical gloves of recent vintage are dusted with starch, talc contamination may still be found.<sup>7</sup> Thus, a history of pelvic operations (appendectomy, cesarean section, hysterectomy, and other operations on internal genital organs other than bilateral salpingo-oophorectomy) was determined in cases and controls. Excluding operations associated with the diagnosis or treatment of the ovarian cancer among the cases, no excess in the occurrence of pelvic operations was noted. The greatest opportunity for talc exposure from surgery occurred before 1950, when talc was the

TABLE 2. Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Potential Talc Exposure from Contamination on Rubber Products

Exposure	Cases		Controls		Crude RR	Adjusted RR*	95% Confidence limits
	Total	No. (%) with exposure	Total	No. (%) with exposure			
Pelvic surgery	215	78 (36.3)	215	75 (34.9)	1.06	1.17	(0.76-1.79)
Pelvic surgery (prior to 1950)	215	51 (23.7)	215	48 (22.3)	1.08	1.12	(0.69-1.82)
Use of condom†	169	19 (11.2)	191	30 (15.7)	0.68	0.77	(0.41-1.44)
Use of diaphragm†	169	37 (21.9)	191	35 (18.3)	1.24	1.19	(0.69-2.05)

\* Adjusted for parity (nulliparous, parous) and menopausal status (pre- and postmenopausal).

† Restricted to subjects who had ever been married.

TABLE 3. Relative Risks (RR) Associated with Using Talc for Storage Among Diaphragm Users\* by Duration of Use of Diaphragm

Duration of diaphragm use	Total	Cases		Controls		Crude RR	Adjusted RR†	95% Confidence limits
		No. (%) who used talc on diaphragm	Total	No. (%) who used talc on diaphragm	Total			
Total diaphragm use less than five years	13	6 (46.2)	21	8 (38.1)	21	1.39	1.82	(0.42-8.00)
Total diaphragm use five or more years	27	16 (59.3)	19	11 (57.9)	19	1.06	1.23	(0.36-4.17)
All users	40	22 (55.0)	40	19 (47.5)	40	1.35	1.56	(0.62-3.88)

\* Includes all women who used diaphragm regardless of marital status.

† Adjusted for parity and menopausal status.

predominantly used dusting powder for surgical gloves. However, no significant excess of pelvic operations prior to 1950 was observed for cases.

The patients (cases) who, at sometime, had been married, chose condoms less frequently and diaphragms more frequently for contraception than the control group, but neither difference was statistically significant. Condom use is not necessarily associated with talc exposure. Not all brands of condoms are dusted with talc, and lubricants could affect the shedding of talc from the condom. Unfortunately, details on specific brands of condoms were not obtained. Similarly, talc exposure is not a necessary consequence of diaphragm use. We inquired specifically about the practice of dusting the diaphragm with talc for storage after use (Table 3). Among all subjects who had used a diaphragm, there was no significant excess of cases who regularly stored their diaphragm using talc, nor was any greater risk associated with this practice observed among women who had used the diaphragm for longer durations. Before the risk from this exposure can be adequately assessed, greater detail is needed including frequency of use and whether the powder was washed off prior to use. Furthermore, contraceptive jellies used with the diaphragm could affect the transport of talc in the genital tract.

Hygienic practices involving talc were also studied. Specifically, we inquired whether women had regularly used talc as a dusting powder on the perineum or regularly dusted sanitary napkins with talc (Table 4). Ninety-two (42.8%) of the cases had talc exposure by either or both of these routes compared with 61 (28.4%) of the controls. The adjusted relative risk was 1.92 ( $P < 0.003$ ) with 95% confidence limits of 1.27-2.89 compared to subjects who had neither exposure. Sixty (27.9%) cases and 48 (22.3%) controls had either used talc for dusting or on napkins but not both. This difference yielded an adjusted relative risk of 1.55, which was of borderline significance ( $P = 0.06$ ). The greatest risk occurred in women who had both exposures (use on the perineum and on napkins) compared to women who had neither exposure. Thirty-two (14.9%) of cases were in this category compared with 13 (6.0%) controls, for an adjusted relative risk of 3.28 ( $P < .001$ ) and 95% confidence limits of 1.68-6.42. The histologic characteristics of tumors developing in women with perineal exposure to talc did not differ significantly from those in women without perineal exposure to talc (Table 5). In addition, the proportion of cases with tumors of borderline malignancy was identical among those with and without perineal exposure to talc. Twenty-two (18%) of 123 cases without the exposure had tumors of bor-

TABLE 4. Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Talc Exposure in Perineal Hygiene

	No perineal exposure	Any perineal exposure	Types of perineal exposure		
			As dusting powder but not on napkins	On napkins but not as dusting powder	Both on napkins and as dusting powder
Cases (Total = 215)	123 (57.2%)	92 (42.8%)	43 (20.0%)	17 (7.9%)	32 (14.9%)
Controls (Total = 215)	154 (71.6%)	61 (28.4%)	34 (15.8%)	14 (6.5%)	13 (6.0%)
Crude rr	1	1.89	1.58	1.52	3.08
Adjusted RR*	—	1.92	1.55		3.28
95% confidence limits	—	(1.27-2.89)	(0.98-2.47)		(1.68-6.42)

\* Adjusted for parity and menopausal status.

derline malignancy compared to 17 (18%) of 92 with the talc exposure.

### Discussion

The argument linking talc and ovarian cancer includes four elements: the chemical relationship between talc and asbestos, asbestos as a cause of pleural and peritoneal mesotheliomas, the possible relation between epithelial ovarian cancers and mesotheliomas, and the ability of talc to enter the pelvic cavity. The mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them. Generic "talc" is seldom pure and may be contaminated with asbestos, particularly in powders formulated prior to 1976.<sup>8,9</sup>

Epidemiologic studies have clearly linked lung cancer and pleural and peritoneal mesotheliomas with asbestos exposure.<sup>10</sup> An excess of similar pulmonary lesions has been reported in talc workers and seems to be correlated with the amount of asbestos contamination in the talc deposits worked.<sup>11</sup> Graham and Graham<sup>1</sup> were able to induce ovarian neoplasms in guinea pigs with asbestos and suggested that ovarian cancer could be related to asbestos exposure, noting the similarity between mesotheliomas and ovarian cancers. Parmley and Woodruff<sup>12</sup> further emphasized this similarity and popularized the pelvic contamination theory, which proposed that environmental carcinogens might enter the pelvic cavity via the genital tract. Years earlier it had been observed that inert carbon particles placed in the vagina immediately prior to hysterectomy could be recovered from the fallopian tubes.<sup>13</sup> Although greeted with skepticism, the finding of talc particles embedded in normal and abnormal ovaries suggests that talc is a substance that can enter the pelvic cavity via the vagina.<sup>2</sup>

Although no consensus concerning the risks of talc has emerged from letters, editorial and articles,<sup>3,14-16</sup> participants in the discussion have agreed upon the need for epidemiologic studies of ovarian cancer and talc exposure. In this case-control study of ovarian cancer of the epithelial variety, we investigated several sources of potential talc exposure. Among these, the only significant finding was an association between ovarian cancer and hygienic practices involving the use of talc on the perineum. It is especially notable that women who regularly had both dusted their perineum with talc and had used it on sanitary napkins had more than a three-fold increase in risk compared to women with neither exposure. Several potential biases must be considered in interpreting this association.

The observation by Wynder *et al.*<sup>17</sup> that menstrual characteristics may differ between women with ovarian cancer and controls might suggest that such differences may confound the association between perineal use of

TABLE 5. Characteristics of Ovarian Cancer in Women with and without Perineal Exposure to Talc

	No perineal use of talc	Any perineal use of talc
	No. (%)	No. (%)
Serous	66 (53.7)	45 (48.9)
Mucinous	16 (13.0)	14 (15.2)
Endometrioid and clear cell	32 (26.0)	24 (26.1)
Other and undifferentiated	9 (7.3)	9 (9.8)
Total	123 (100)	92 (100)

talc and ovarian cancer. We found that menstrual characteristics of cases and controls were virtually identical in this study. Fifty-three (24.7%) cases complained of moderate or severe dysmenorrhea compared to 56 (26.0%) controls. Twenty-five (11.6%) cases complained of irregular periods compared to 32 (14.9%) controls. The average numbers (and SEM) of days of flow and cycle length were, respectively, 4.9 (0.1) and 28.9 (0.3) days for cases and 4.9 (0.1) and 29.6 (0.3) days for controls.

Since entry of talc into the pelvic cavity is prevented by hysterectomy or tubal ligation, it might also be argued that the inclusion of subjects with pelvic surgery in the analysis may obviate any association between talc and ovarian cancer. It should be noted that such surgery generally occurred near the end of reproductive life for both cases and controls, probably after most significant talc exposure had already occurred. The exclusion of such subjects from the analysis did not substantially alter the observed associations. For example, the adjusted relative risk for the use of talc both on the perineum and sanitary napkins was 2.79 ( $P < 0.003$ ) in the group without pelvic surgery compared to 3.28 observed for the entire group.

In terms of other confounders, the association persisted after adjustment for menopausal status and parity. We also applied multivariate logistic regression for paired observations.<sup>6</sup> The maximum likelihood estimate of relative risk associated with any perineal use of talc was 1.61 ( $P = 0.03$ ) with 95% confidence limits of 1.04–2.49 after simultaneous adjustment for religion, marital status, educational level, ponderal index, age at menarche, exact parity, oral contraceptive or menopausal hormone use, and smoking.

Our sample of cases represents more than 50% of ovarian cancer cases diagnosed in Boston residents in the study period. Therefore, it is difficult to conceive of a plausible bias in the selection of cases that would yield this excess use of talc. There is reason for concern that the high refusal rate among the controls may have introduced a selection bias among the controls. But,



when we restricted the analysis to the 121 cases who were matched without a control refusal, we again found a significant association between talc use and ovarian cancer. For women who had used talc both in dusting and on the perineum we found an adjusted relative risk of 2.44 ( $P < 0.05$ ). Interviewer bias is also unlikely to explain the association. Of the 18 women who were initially interviewed as ovarian cancer cases but later excluded as having metastatic tumors to the ovary, only one (5.6%) had both perineal and napkin exposure as compared with 15% in cases and 6% in controls.

Experimental data which might bear on the carcinogenicity of talc come primarily from models using pleural implantation of various minerals in rats.<sup>18</sup> These data suggest that carcinogenicity is dependent primarily upon the shape of the particles with long thin fibers such as those occurring in crocidolite asbestos being most carcinogenic. Talc consists primarily of plates but may contain fibers, although voluntary guidelines to limit the content of asbestiform fibers in consumer talcums were proposed by the cosmetics industry in 1976.<sup>19</sup>

If talc is involved in the etiology of ovarian cancer, it is not clear whether this derives from the asbestos content of talc or from the uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates. With ovulation entrapment of the surface epithelium of the ovary into the ovarian stroma occurs. If present, talc or other particulates might be incorporated into these inclusion cysts. Apparently implantation of foreign bodies into the lumens of epithelial lined organs provides a favorable environment for carcinogenesis.<sup>20</sup> Alternatively, talc might serve to stimulate entrapment of the surface epithelium and act in the same way that "incessant ovulation" has been proposed as an etiologic factor for ovarian cancer.<sup>21</sup> Given the histologic and clinical diversity of ovarian cancer, talc exposure is unlikely to be the only cause. Undoubtedly, reproductive experiences such as pregnancies and, perhaps, oral contraceptive use play a role in its etiology.<sup>21-23</sup> The possibility that talc exposure interacts with these variables deserves further investigation.

It is hoped that this report will stimulate further study of talc exposure in relation to ovarian cancer. Animal studies would be helpful to determine whether and under what circumstances ovarian tumors may be induced by various talc preparations. Epidemiologic studies should focus on opportunities for excessive vaginal contamination with talc such as when it is repeatedly used in perineal dusting powders or sprays and in or on tampons, sanitary napkins, or other products intended for

intravaginal use. More precise details on the exact nature and frequency of the exposure and the amount and specific brand of powder used are essential. Opportunities for talc exposure are widespread and pervasive,<sup>24</sup> but that should not discourage epidemiologists from studying this potentially important exposure in relation to ovarian cancer.

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**TALCUM COMPANY CALLS STUDY ON CANCER LINK INCONCLUSIVE**

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**TEXT:**

A major talcum powder manufacturer, while criticizing a recent study linking the use of talcum powder by women to ovarian cancer, said it would further investigate any possible relationship between cosmetic-grade talc and the development of disease.

**The study, published in the Aug. 15 issue of the journal Cancer**, found that women who dusted their genitals and sanitary napkins with talcum powder were three times as likely to develop cancer as women who did not.

The cases studied involved 215 women diagnosed as having ovarian cancer in Boston hospitals from November 1978 to September 1981. About 43 percent of the women said they dusted talc on their genitals or on sanitary napkins, s against about 28 percent of a control group of similar background, age and marital status who said they did not use talc .

But the principal author of the study, Dr. Daniel W. Cramer, an obstetrician and gynecologist, said further studies would be needed before doctors could recommend that women avoid using talc . In a statement released by Brigham and Women's Hospital in Boston, Dr. Cramer said, "It is hoped that this report will stimulate further study of talc exposure in relation to ovarian cancer."

**Questioned About Current Use**

James Murray, a public relations officer for **Johnson & Johnson**, a talcum powder manufacturer, said the study was inconclusive because it had asked the women about current use of talc rather than about use over a period of years, when they would have been developing the cancers.

But he added: "We agree more study is needed, and we are going to conduct appropriate new studies. We feel there is a vast amount of published research on talc in humans and animals that has shown no tendency of pure cosmetic-grade talc to cause cancer."

Dr. Cramer's study suggested that contamination of the talc might have caused the cancers. "If talc is involved in the etiology of ovarian cancer," it said, "it is not clear whether this derives from the asbestos content of talc or some uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates." Most baby powder is made essentially of talc .

In the 1970's talc , a mineral mined widely in Europe, Canada and the United States, was often found to be contaminated with asbestos, a known cause of cancer. For instance, researchers at Mount Sinai Medical Center in New York found asbestos in 10 of 20 samples of cosmetic talc taken before 1973.

The industry was informed of these and similar findings and is believed

to have changed its methods and sources of mining. Mr. Murray of Johnson & Johnson said, "We can confirm that our talc doesn't contain any asbestos."

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DESCRIPTORS: CONSUMER PROTECTION; RESEARCH; CANCER; WOMEN;  
COSMETICS





**FOR IMMEDIATE RELEASE**

**PETITION SEEKS A CANCER WARNING ON COSMETIC TALC PRODUCTS**

**Petition Seeks a Cancer Warning on Cosmetic Talc Products**

**CHICAGO, IL, May 15, 2008 --/WORLD-WIRE/--** A coalition of public health experts, medical doctors and consumers organizations is petitioning the U.S. Department of Health and Human Services and the Food and Drug Administration for labels on talcum powder products warning that frequent use is linked to ovarian cancer.

The petition addresses Secretary of Health and Human Services Mike Leavitt, and Commissioner of Food and Drugs Andrew C. von Eschenbach, M.D., a former director of the National Cancer Institute.

The group seeks labels with a warning such as, "Frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer," on all cosmetic talcum products. The petition also seeks a public hearing at which evidence can be presented that the genital application of talc can result in its translocation to the ovary.

The Citizen Petition is submitted on behalf of: Samuel S. Epstein, M.D., Chairman, Cancer Prevention Coalition (CPC), and Professor emeritus Occupational and Environmental Medicine, University of Illinois at Chicago School of Public Health; Peter Orris, M.D., Professor and Chief of Service, University of Illinois at Chicago Medical Center; Quentin Young, M.D., Chairman, Health and Medicine Policy Research Group, Chicago; Rosalie Bertell, Ph.D., International Association for Humanitarian Medicine, Scientific Advisor to the International Institute of Concern for Public Health, Toronto, and the International Science Oversight Board of the Organic Consumers Association, Washington, D.C.; and Ronnie Cummins, National Director of the Organic Consumers Association.

This is not the first petition seeking such warning labels. On November 17, 1994, the Cancer Prevention Coalition and the New York Center for Constitutional Rights submitted a Citizen Petition to the Commissioner of the FDA, "Seeking Carcinogenic Labeling on all Cosmetic Talc Products."

The scientific basis of the 1994 Petition was admitted by the industry. In an August 12, 1982, article in the New York Times, Johnson & Johnson, the manufacturer and retailer of talc dusting powder, stated it was aware of a publication which concluded that frequent genital application of talc was responsible for a three-fold increased risk of ovarian cancer.

**PETITION SEEKING A CANCER WARNING ON COSMETIC TALC PRODUCTS**

**May 13, 2008**

**Mike Leavitt**  
**Secretary of Health and Human Services**  
**U.S. Department of Health and Human Services**

**Andrew C. von Eschenbach, M.D.**  
**Commissioner of Food and Drugs**

**Dockets Management Branch**  
**Food and Drug Administration, Room 1601**  
**5630 Fishers Lane**  
**Rockville, MD 20852**

**This Petition, submitted under 21 U.S.C. 321 (n), 361, 362, and 371 (a); and 21 CFR 740.1, 740.2 of 21 CFR 10.30 of the Federal Food, Drug and Cosmetic Act, requests the Commissioner of Food and Drugs to require that all cosmetic talc products bear**

labels with a warning such as, "Frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer."

#### **A. AGENCY ACTION REQUESTED**

This Petition requests FDA to take the following action:

(1) Immediately require cosmetic talcum powder products to bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer."

(2) Pursuant to 21 CFR 10.30 (h) (2), a hearing which will be held at which time we can present scientific evidence in support of this Petition.

#### **B. STATEMENT OF GROUNDS**

On November 17, 1994, the Cancer Prevention Coalition and the New York Center for Constitutional Rights submitted a Citizen Petition to the Commissioner of the FDA, "Seeking Carcinogenic Labeling on all Cosmetic Talc Products."

The Petition was endorsed by Quentin Young, M.D., Chairman of The Health and Medicine Policy Research Group, Peter Orris, M.D., Director of Health Hazard Evaluation, Cook County Hospital, and Professor of Medicine, University of Illinois Medical School, Chicago, Nancy Nelson, Chair of the Ovarian Cancer Early Detection and Prevention Foundation, and subsequently by Senator Edward Kennedy. In a 1997 statement to the Senate, he requested the FDA to place a cancer warning on the label of talc products, besides other products containing known carcinogens. However, over a decade later his warning remains ignored.

The 1994 Petition was supported by 15 scientific publications. These included nine, from 1983 to 1992, on the major risks of ovarian cancer from the frequent application of brand or generic talc "baby powder" to the genital area of women without any warning of the risks involved. Two of these publications also reported that the genital application of talc could result in its translocation to the ovary.

The scientific basis of the 1994 Petition was further supported by J. Mande, Acting Associate Commissioner for Legislative Affairs of the Department of Health and Human Services. On August 25, 1993, he admitted that "We are aware that there have been reports in the medical literature between frequent direct female perineal talc dusting over a protracted period of years, and an incremental increase in the statistical odds of subsequent development of certain ovarian cancers ... (However) at the present time, the FDA is not considering to ban, restrict or require a warning statement on the label of talc containing products."

The scientific basis of the 1994 Petition was also admitted by the industry. In an August 12, 1982, article in the New York Times, Johnson & Johnson, the manufacturer and retailer of talc dusting powder, stated it was aware of a publication which concluded that frequent genital application of talc was responsible for a three-fold increased risk of ovarian cancer.

Warnings of these risks were emphasized by the Cancer Prevention Coalition in November 19, 1994, in letters to Mr. Ralph Larsen, CEO of Johnson & Johnson, and Mr. C.R. Walgreen, Chairman and CEO of Walgreens. Johnson & Johnson was urged to substitute cornstarch, a safe organic carbohydrate, for talcum powder products, and also to label its products with a warning on cancer risks.

In spite of the scientific evidence, and admission by Johnson & Johnson, the Petition was denied by Dr. John Bailey, FDA's Director of the Office of Cosmetics and Colors, on the basis of the "limited availability" (of Agency resources) and on alleged scientific grounds. Dr. Bailey is currently Director of the industry's Personal Care Products Council.

Evidence for the May 2008 Petition is supported by Edward Kavanaugh, President of the industry's Cosmetic Toiletry and Fragrance Association. In 2002, he admitted that talc is "toxic," that it "can reach the human ovaries," and that prior epidemiological investigations concluded that its genital application increased the risk of ovarian cancer.

Further evidence for this Petition is based on 12 publications since 1995, cited below. These confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As Dr. Andrew C. von Eschenbach, former Director of the National Cancer Institute, is aware, the mortality of ovarian cancer for women over the age of 65, has escalated dramatically since 1975, by 13% for white and 47% for black women (1). There are about 15,300 deaths from ovarian cancer each year. This makes it the fourth most common fatal cancer in women after colon, breast and lung.

A case-control study, the largest to date, confirmed the relation between the perineal use of talc and ovarian cancer (2). This has also been confirmed by other reports (3-7). In view of the strength of this evidence, "formal public health warnings" were urged in 1999 (8).

An analysis of 16 pooled studies confirmed a statistically significant 33% increased risk of ovarian cancer associated with the perineal use of talc (9). A report by 19 scientists in eight nations worldwide, under the auspices of the International Agency for Research on Cancer, concluded that eight publications confirmed a 30-60% increased risk of ovarian cancer following the perineal application of talc (10). This risk has been confirmed in other reports (11, 12).

The protective effects of tubal ligation or hysterectomy, preventing the translocation of talc from the perineum to the ovary, have also been confirmed (2, 3, 4, 7).

#### **C. CLAIM FOR CATEGORICAL EXCLUSION**

A claim for categorical exclusion is asserted pursuant to 21 CFR 25.24 (a) (11).

#### **D. CERTIFICATION**

The undersigned certifies, that, to his best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

#### **This petition is submitted by:**

Samuel S. Epstein, M.D.

Chairman, Cancer Prevention Coalition

Professor emeritus Occupational and Environmental Medicine

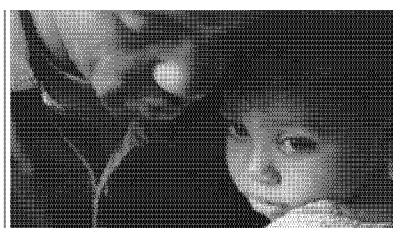
University of Illinois School of Public Health, Chicago

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## Cancer Prevention Coalition

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Press Room

### Citizen Petition Seeking Carcinogenic Labeling on All Cosmetic Talc Products

November 17, 1994

David A. Kessler, M.D.  
Commissioner  
Food and Drug Administration, Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

The undersigned submits on behalf of the Cancer Prevention Coalition, Inc. (CPC), Samuel S. Epstein, M.D., Chair and National Advisor of the Ovarian Cancer Early Detection and Prevention Foundation (OCEDPF), Nancy Nehls Nelson, member of the Ovarian Cancer Early Detection and Prevention Foundation, Peter Orris, M.D. and Quentin Young, M.D. This citizen petition is based on scientific papers dating back to the 1960s which warn of increased cancer rates resulting from frequent exposure to cosmetic grade talc.

The undersigned submits this petition under 21 U.S.C. 321 (n), 361, 362, and 371 (a); and 21 CFR 740.1, 740.2 of 21 CFR 10.30 of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to require that all cosmetic talc products bear labels with a warning such as Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases risk of ovarian cancer.

#### A. AGENCY ACTION REQUESTED

This petition requests that FDA take the following action:

(1) Immediately require cosmetic talcum powder products to bear labels with a warning such as Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer.

(2) Pursuant to 21 CFR 10.30 (h) (2), a hearing at which time we can present our scientific evidence.

#### B. STATEMENT OF GROUNDS

Ovarian cancer is the fourth deadliest women's cancer in the U.S., striking approximately 23,000 and killing approximately 14,000 women this year. Ovarian cancer is very difficult to detect at the early stages of the disease, making the survival rate very low. Only three percent of ovarian cancer cases can be attributed to family history. (1) One of the avoidable risk factors for ovarian cancer is the daily use of talcum powder in the genital area. (2)

Research done as early as 1961 has shown that particles, similar to talc

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and asbestos particles, can translocate from the exterior genital area to the ovaries in women. (3,4,5) These findings provide support to the unexpected high rate of mortality from ovarian cancer in female asbestos workers. (6,7,8) Minute particles, such as talc are able to translocate through the female reproductive tract and cause foreign body reactions in the ovary.

There is a large body of scientific evidence, dating back thirty years, on the toxicity and mineralogy of cosmetic talc products. As early as 1968, Cralley et al. Concluded:

All of the 22 talcum products analyzed have a ...fiber content...averaging 19%. The fibrous material was predominantly talc but probably contained minor amounts of tremolite, anthophyllite, and chrysotile [asbestos-like fibers] as these are often present in fibrous talc mineral deposits...Unknown significant amounts of such materials in products that may be used without precautions may create an unsuspected problem. (9)

As a follow-up to previous findings, Rohl, et al., examined 21 samples of consumer talcums and powders, including baby powders, body powders, facial powders and pharmaceutical powders between 1971-1975. The study concluded:

...cosmetic grade talc was not used exclusively. The presence in these products of asbestiform anthophyllite and tremolite, chrysotile, and quartz indicates the need for a regulatory standard for cosmetic talc...We also recommend that evaluation be made to determine the possible health hazards associated with the use of these products. (11,10)

Talc is a carcinogen, with or without the presence of asbestos-like fibers. In 1993, the National Toxicology Program published a study on the toxicity of non-asbestiform talc and found clear evidence of carcinogenic activity (11).

Recent cancer research in the United States has found conclusively that frequent talcum powder application in the genital area increases a woman's risk of developing ovarian cancer (12,13,14,15).

Cramer, et al, suggested that talc application directly to the genital area around the time of ovulation might lead to talc particles becoming deeply imbedded in the substance of the ovary and perhaps causing foreign body reaction (granulomas) capable of causing growth of epithelial ovarian tissue (16,17).

Harlow, et al, found that frequent talc use directly on the genital area during ovulation increased a woman's risk **threefold**. That study also found:

"The most frequent method of talc exposure was use as a dusting powder directly to the perineum (genitals) . . . Brand or generic 'baby powder' was used most frequently and was the category associated with a statistically significant risk for ovarian cancer."

In Harlow's report, arguably the most comprehensive study of talc use and ovarian cancer to date, 235 ovarian cancer cases were identified and compared to 239 controls, women with no sign of ovarian cancer or





related health problems. Through personal interviews, Harlow, et al, found that 16.7% of the control group reported frequent talc application to the perineum (18). This percentage is useful in estimating the number of women in the general population exposed to cosmetic talc in the genital area on a regular basis. Harlow, et al, concludes:

“... given the poor prognosis for ovarian cancer, any potentially harmful exposures should be avoided, particularly those with limited benefits. For this reason, we discourage the use of talc in genital hygiene, particularly as a daily habit.”

Clearly, large numbers of women—an estimated 17%—are using cosmetic talc in the genital area and may not be adequately warned of the risk of ovarian cancer from daily use.

### **C. CLAIM FOR CATEGORICAL EXCLUSION**

A claim for categorical exclusion is asserted pursuant to 21 CFR 25.24 (a) (11).

### **D. CERTIFICATION**

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

This petition is submitted by:

Jill A. Cashen  
Samuel S. Epstein, M.D.  
Cancer Prevention Coalition

Michael E. Deutsch, Legal Director  
Center for Constitutional Rights

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#### **APPENDIX I: Results for an informal survey of talc products in Chicago drug stores.**

##### **BABY POWDERS**

Johnson & Johnson Baby Powder. Contains: TALC, fragrance.

Osco Brand Baby Powder. Contains: TALC, fragrance.

Jean Nate Perfumed Talc. Contains: TALC, kaolin, magnesium carbonate, fragrance.

Shower to Shower. Contains: TALC, cornstarch, sodium bicarbonate, fragrance, polysaccharides.

Ammens Medicated Powder. Contains: Zinc oxide, cornstarch, fragrance, isostearic acid, PPG-20, methyl glucose ether, TALC.

Cashmere Bouquet Perfumed Powder. Contains: TALC, magnesium carbonate, zinc stearate, fragrance.

Gold Bond Medicated Powder. Contains: Menthol, zinc oxide, boric acid, eucalyptol, methyl salicylate, salicylic acid, TALC, thymol, zinc stearate.

##### **FEMININE PRODUCTS**

Vagisil Feminine Powder. Contains: Cornstarch, aloe, mineral oil, magnesium stearate, silica, benzethonium chloride, fragrance.

Vaginex Feminine Powder. Contains: Zinc oxide, cornstarch, fragrance, 6-hydroxquinoline, 8-hydroxquinoline sulfate, isostearic acid, PPG-20, methyl glucose ether, TALC.

Summer's Eve Feminine Powder. Contains: Cornstarch, tricalcium phosphate, oxoynol-9, benzethonium chloride, fragrance.

FDS Feminine Deodorant Spray. Contains: Isobutane, isopropyl myristate, cornstarch, mineral oil, fragrance, lanolin alcohol, hydrated

silica, magnesium stearate, benzyl alcohol.

**From:** Wille, Kathleen K. [CPCUS]  
**Sent:** 5/20/2008 7:29:17 PM  
**To:** Wille, Kathleen K. [CPCUS] ; Musco, Nancy [CPCUS] ; Kurtz, Ellen [CPCUS] ; Paterson, Clayton H. [JJCUS] ; Grossman, Iris [CPCUS] ; McCarthy, Timothy [CPCUS]  
**Subject:** Formal J&J Response to Citizen's Petition  
**Location:** CPC CONF RM/SK SA-302 (8), [CPCUS]  
**Start:** Tue 5/27/2008 3:00:00 PM  
**End:** Tue 5/27/2008 4:00:00 PM  
**Recurrence:** (none)  
**Meeting Status:** Accepted

**Required Attendees:** Musco, Nancy [CPCUS]; Kurtz, Ellen [CPCUS]; Paterson, Clayton H. [JJCUS]; Grossman, Iris [CPCUS]; McCarthy, Timothy [CPCUS]; CPC CONF RM/SK SA-302 (8), [CPCUS]  
**Optional Attendees:** Nettesheim, Susan [CPCUS]  
**Attachments:** Citizen's Petition nov17\_94.pdf; NYTimes 1982 Story.doc; Press Release and Cit Petition May 2008.doc; Talc Aug 1982 article in Cancer.pdf

All,

This meeting is so that we can start our conversation on responding formally to the docket regarding the most recent Citizen's petition. It is very hard to get this group of folks together in a reasonable time period, so I hope that you can free up some time to attend, if you have a conflict. Let me know if I need to set up a call-in number.

Thanks,  
Kathy



Talc Aug 1982 article in Cancer.pdf



NYTimes 1982 Story.doc



Press Release and Cit Petition May 2008.doc



Citizen's Petition nov17\_94.pdf